

## Neutrophil to Lymphocyte Ratio as a Predictor of Endoscopic Damage in Caustic Injuries

Seyit Uyar<sup>\*</sup> and Mehmet Kok

Antalya Training and Research Hospital, Antalya, Turkey

<sup>\*</sup>Corresponding author: Seyit Uyar, Antalya Training and Research Hospital, Antalya, Turkey, Tel: +902422494400; E-mail: seyituyar79@hotmail.com

Received date: April 27, 2017, Accepted date: May 18, 2017, Published date: May 26, 2017

Copyright: © 2017 Uyar S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Context:** The endoscopic degree of injuries is the main finding for further management of caustic ingestions. However, if endoscopy cannot be performed quickly, clinicians decide on treatment and follow-up goals according to the signs and symptoms of the patient. The aim of this study was to determine the association of white blood cells (WBC), C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) with the degree of caustic injury and to evaluate whether NLR is able to predict the severity of injuries.

**Materials and methods:** A retrospective evaluation was made of a total of 190 patients with a mean age of 38.6 years. WBC, neutrophil, lymphocyte and CRP values and endoscopic findings of all patients at hospital admission were retrieved from hospital files. The association between WBC, NLR, CRP and endoscopic findings was evaluated.

**Results:** Endoscopy was normal in 28 of 119 patients (23.5%) and most patients (42 of 119 (35.3%) had only gastric involvement. NLR was significantly higher in patients with injuries than normal patients ( $p=0.010$ ), whereas WBC and CRP not. NLR was also significantly higher in patients with both esophagus and gastric injuries compared to patients with no organ involvement ( $p<0.001$ ). NLR, WBC and CRP were weakly correlated to the grade of involvement. In the ROC analysis, the AUC value was 0.914 (95% CI (0.85-0.96,  $p<0.001$ )) and the cut-off value for NLR was 8.71 with sensitivity of 90% and specificity of 91.7% for discriminating injuries as grade 0-1-2 from 3-4.

**Conclusions:** Higher NLR values showed widespread and severe involvement of caustic ingestion. NLR also seems to be a more reliable method to make a distinction between severe and mild injuries. It is an easily derived and inexpensive marker of inflammation and might guide the management of patients before endoscopic evaluation in emergency departments.

**Keywords:** Neutrophil; Inflammation; Carcinoma; Lymphocyte; Leukocytosis

### Introduction

Caustic injuries remain a medical problem, which can cause serious damage to the gastrointestinal tract. Although mainly seen in children, these injuries can also be seen in adults, both intentionally and accidentally [1]. Caustic ingestion may cause esophageal and gastric superficial edema, erythema, erosions, ulcerations, necrosis and ultimately perforation in the early period [2]. Patients with perforation have to be diagnosed without any loss of time, as immediate surgical intervention may be required [3]. Late sequelae of caustic injuries include strictures in the esophagus and stomach, gastric outlet obstruction, mucosal metaplasia and carcinoma [4]. These complications of caustic injuries are detected with upper gastrointestinal endoscopy and endoscopic findings are the major predictor of the formation of late complications [2,5]. However, endoscopy is not always feasible especially in developing countries where these events are common. The laboratory tests [6], computed tomography [7] and endoscopic ultrasound [8] were used for this purpose in different studies. White blood cell count (WBC), C-reactive protein (CRP), and arterial blood gas analysis are laboratory tests used in a few studies for prediction of degree of caustic injury and of late

seques. For example, Cheng et al. evaluated arterial blood gas analysis in caustic ingestions and concluded that arterial  $pH<7.22$  or base excess  $<-12$  indicate severe esophageal injury and the need for emergency surgery [9].

The neutrophil-lymphocyte ratio (NLR) is a method which is cost effective and readily available and could be an important measure of systemic inflammation [10]. It is used as an inflammatory marker in various diseases such as cancer, inflammatory disorders, hypertension, diabetes, obesity, hyperlipidemia and vascular diseases [10,11]. Elevated NLR levels are associated with poor survival and increased morbidity in various chronic conditions [12]. Elevated NLR levels have been associated with poor survival of patients undergoing coronary bypass surgery [13] and any cancer survival studies have also shown that NLR can be a significant predictor of overall and disease-specific survival of patients [14-16].

The aim of this study was to determine the WBC, NLR and CRP values of patients with corrosive injuries and to assess the correlation of these acute phase parameters with organ involvement and the degree of injury. It was also evaluated whether NLR could predict the endoscopic degree of caustic injuries.

## Methods

A retrospective evaluation was made of patients with a diagnosis of corrosive ingestion admitted to the University of Health Sciences Antalya Training and Research Hospital between 2008 and 2016. WBC, neutrophil, lymphocyte and CRP values and the endoscopic findings of all patients at hospital admission were retrieved from hospital files. Since CRP of all patients were not tested, totally 67 patients were evaluated for CRP. Patients were excluded if endoscopy had not been applied, or if endoscopy was applied after 96 hours and without laboratory tests within the first six hours of hospital admission. Patients under the age of 18 years were also excluded from the study. The association between WBC, NLR, CRP and endoscopic findings was evaluated. The endoscopic classification of caustic injuries is shown in Table 1 [17].

Grade	Features
Grade 0	Normal
Grade 1	Superficial mucosal edema and erythema
Grade 2	Mucosal and submucosal ulcerations
Grade 2A	Superficial ulcerations, erosions, exudates
Grade 2B	Deep discrete or circumferential ulcerations
Grade 3	Transmural ulcerations with necrosis
Grade 3A	Focal necrosis
Grade 3B	Extensive necrosis
Grade 4	Perforations

**Table 1:** Endoscopic classification of caustic injuries.

The study protocol was applied in accordance with the principles of the Declaration of Helsinki. Approval for the study was granted by the Local Research Institutional Ethics Committee.

## Results

A total of 190 patients (58 male, 61 female) with a mean age of 38.6 ± 15 years (range, 18-79 years) were evaluated. The median WBC count was 9 10<sup>3</sup>/mm<sup>3</sup> (2.8-31 10<sup>3</sup>/mm<sup>3</sup>), median CRP level was 3 mg/dL (1-174 mg/dL), median neutrophil count was 5.6 10<sup>3</sup>/mm<sup>3</sup> (1.3-27.9 10<sup>3</sup>/mm<sup>3</sup>), median lymphocyte count was 2.1 10<sup>3</sup>/mm<sup>3</sup> (0.4-5.2 10<sup>3</sup>/mm<sup>3</sup>) and median NLR was 2.7 (0.8-32.8). Endoscopy was normal in 28 of 119 patients (23.5%). Involvement was only esophageal in 12 (10.1%) patients, only gastric in 42 (35.3%) and both esophageal and gastric in 37 (31.1%) (Table 2).

Of the esophagus involved patients, 30 (61.2%) were grade 1, 15 (30.6%) were grade 2a, 3 (6.1%) were grade 2b, and 1 (2%) was grade 3a. Of the gastric involved patients, 55 (69.6%) were grade 1, 8 (10.1%) were grade 2a, 6 (7.6%) were grade 2b, 7 (8.8%) were grade 3a, 2 (2.5%) were grade 3b, and 1 (1.2%) was grade 4 (Table 2).

Age (years), mean ± sd		
38.6 ± 15		
Gender, n (%)	Male	58 (48.7)

	Female	61 (51.3)
		9 (2.8-3.1)
WBC (10 <sup>3</sup> /mm <sup>3</sup> ), median (min-max)	Neutrophil	5.6 (1.3-27.9)
	Lymphocyte	2.1 (0.4-5.2)
NLR, median (min-max)		2.7 (0.8-32-8)
CRP (mg/dL), median (min-max)		3 (1-174)
Caustic ingestion characteristics		
Organ involvement, n (%)	None	28 (23.5)
	Esophagus	12 (10.1)
	Stomach	42 (35.3)
	Esophagus+stomach	37 (31.1)
Grade of esophageal injury (n: 49), n (%)	Grade 1	30 (61.2)
	Grade 2a	15 (30.6)
	Grade 2b	3 (6.1)
	Grade 3a	1 (2)
	Grade 3b	0
	Grade 4	0
	Grade of gastric injury (n: 79), n (%)	Grade 1
Grade 2a		8 (10.1)
Grade 2b		6 (7.6)
Grade 3a		7 (8.8)
Grade 3b		2 (2.5)
Grade 4		1 (1.2)
WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, CRP: C-reactive protein		

**Table 2:** Patient demographic characteristics, involved organs and endoscopic grade of the injury.

The comparisons of the WBC, NLR and CRP values between injured and non-injured patients are shown in Table 3. WBC (9.1(2.8-31) vs. 8.75(6.7-15.5), p=0.573) and CRP (3(1-174) vs. 3(1-39), p=0.166) values were not significantly different in both group. NLR (2.9(1.02-32.8) vs. 2.2(0.8-11.8), p=0.010) was significantly higher in injured patients than normals. with organ involved than non-involved patients NLR (5(1.4-32.8) vs. 2.2(0.8-11.8), p<0.001) was significantly higher in patients with esophagus and gastric involvement compared to non-involved patients.

	Injured patients	Non-injured patients	P*
CRP (mg/dL)	3 (1-174)	3 (1-39)	0, 166
n	n:52	n:15	

WBC (10 <sup>3</sup> )	9, 1 (2, 8-3, 1)	8, 75 (6, 7-15, 5)	0, 473
n	n:91	n:28	
NLR	2, 9 (1, 02-32, 8)	2, 2 (0, 8-11, 8)	0, 010
n	n:91	n:28	
<b>Comparison of NLR values according to location of injury</b>			
Esophagus (n:12)	2, 7 (1, 4-14, 8)		0, 199
Stomach (n:42)	2, 29 (1, 02-26)	2, 2 (08-11, 8)	0, 283
Esophagus+ Esophagus (n: 37)	5 (1, 4-32, 8)		0, 001

**Table 3:** Comparison of WBC, NLR and CRP values between injured and non-injured patients and comparison of NLR values according to location of injury.

There were no significant differences between patients with only esophagus or stomach involvement compared to non-involved patients in terms of NLR (Table 3).

All the variables (WBC (r=0.43, p=0.006), NLR (r=0.43, p<0.001) and CRP (r=0.29, p=0.019)) were determined to be weakly correlated to the grade of involvement (Table 4).

	Grade of injury	
	r <sup>*</sup>	p
NLR	0.43	<0.001
WBC (10 <sup>3</sup> /mm <sup>3</sup> )	0.25	0.006
CRP (mg/dL)	0.29	0.019
*Spearman's rho		
WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, CRP: C-reactive protein		

**Table 4:** Correlation between endoscopic grade of injury and NLR, WBC and CRP values.

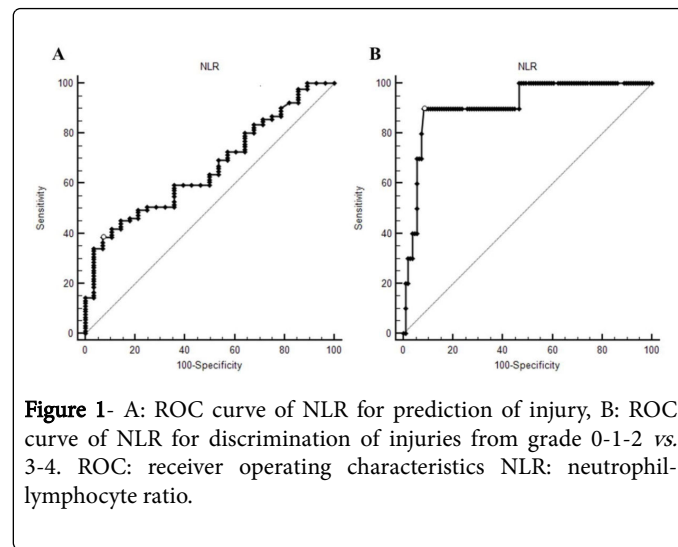
ROC analysis was applied for the prediction of the grade of caustic injuries as 0 vs. 1-2-3-4 and as 0-1-2 vs. 3-4. The AUC (area under curve) value was 0.66 (95% CI (0.57-0.75, p=0.003) for prediction of the prsence of injury (Figure 1A) and the cut-off value for NLR was 2.56 with a sensitivity of 59.34% and specificity of 64.29% (Table 5).

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
NLR (Grade 0 vs. 1-2-3-4)	0.66, 95% CI (0.57-0.75, p=0.003)	2.56	59.34	64.29
NLR (Grade 0-1-2 vs. 3-4)	0.914, 95% CI (0.85-0.96, p<0.001)	8.71	90	91.7

**Table 5:** Estimates of NLR for discrimination of grade of caustic injuries.

Number of patients with NLR ≤ 2.56 was 55 and it was 64 for NLR>2.56. For discrimination of the grade of injuries as 0-1-2 from

3-4, the AUC value was 0.914 (95% CI (0.85-0.96, p<0.001)) (Figure 1B) and the cut-off value for NLR was 8.71 with sensitivity of 90% and specificity of 91.7% (Table 5). Number of patients with NLR >8.71 was 18.



**Figure 1-** A: ROC curve of NLR for prediction of injury, B: ROC curve of NLR for discrimination of injuries from grade 0-1-2 vs. 3-4. ROC: receiver operating characteristics NLR: neutrophil-lymphocyte ratio.

## Discussion

Caustic injuries may lead to irreversible catastrophic complications. Endoscopy is the gold standard for evaluation of caustic ingestions, but it can take time to apply. The initial signs and symptoms of patients are the main factors which determine the treatment and follow-up goals in emergency clinics before endoscopy. Betalli et al. reported that the presence of symptoms was the strongest predictor of severe esophageal lesions in a multi-centre observational study of a pediatric population [18]. Endoscopy is usually recommended in the first 12-48 hours after caustic ingestion [2] and is reliable for up to 96 hours after the injury [17]. The degree of injury determined on endoscopy is the major finding for patient management and prediction of complications. Generally, grade 0 and 1 lesions do not develop sequelae and morbidity and mortality also increase as the degree of injury increases [17]. Patients with grade 1 or 2A injury are permitted oral intake earlier and are generally discharged within days with antacid therapy. Patients with grade 2 or 3 injury however, are more severe cases and may need closer observation and may stay longer in hospital [2]. In the current study, the endoscopic findings of 28 patients (23.5%) were normal and most of the patients (42/119) had gastric involvement. Only 1 patient had a grade 4 gastric injury and a total of 10 patients had grade 3 injury of the esophagus or stomach.

Studies on laboratory values are limited in caustic injuries. In this study, the WBC and CRP values of patients in injured and non-injured group were not significantly different, whereas NLR was significantly higher in injured patients. While the NLR values were not different in the involvement of the esophagus or stomach separately, it was significantly higher in patients with both esophagus and stomach damaged than those of the patients with no organ involvement (p<0.001). In a pediatric population study, WBC count was found significantly more frequent in children with high-grade injury than low-grade injury [19]. The comparison groups were designed differently from ours and mean age of patients was 3.4 in that study. However, in a similar study by Chen et al. [20] found that there was no statistically significant difference in terms of WBC and CRP values

between high-grade and low-grade injuries. In another study in patients with median age 22 years (min:2-max:61), WBC count was higher in high-grade injured patients [21]. Kaya et al. and Chen et al. reported that WBC count could not predict the severity of esophageal injury in these studies; however Hovanond et al. stated that WBC count was an independent predictor for high-grade injury. The prognostic relevance of leukocytosis was suggested another report by Rigo et al. [22]. They suggested that a WBC count  $\geq 20,000$  cells/ $m^3$  should be considered a predictor of a poor outcome. There is no study evaluating NLR value and caustic injuries in the literature.

Although it was a weak correlation, WBC, NLR and CRP values were significantly correlated to the grade of injury in our study. AUC value was less than 80% for NLR greater than 2.56 for discrimination of grade 0 from 1-2-3-4 in ROC analysis. NLR greater than 8.71 was a significantly good diagnostic marker for the differentiation of mild and severe caustic injuries (grade 0, 1, 2 vs. 3, 4) [AUC:0.914, 95% CI (0.85-0.96,  $p < 0.001$ )]. This is a valuable finding for primary physicians in Emergency Departments to be able to plan further management of the patient. However, the number of patients with severe injury (n=10) and NLR > 8.71 (n=18) was low. Because, caustic injuries are mostly seen in developing countries and endoscopy is not readily available and emergency endoscopic grading is the main factor reflecting patient survival and functional outcome [17]. In a study by Cabral et al., most patients with mild injuries (grade I-IIIa) were managed with medical treatment (10/158 patients underwent surgery), whereas most of the patients with severe injuries (grade IIIb-IV) were managed surgically (78/84 patients underwent surgery) [23]. Therefore, according to the results of the current study, patients with NLR values > 8.71 need closer observation and further evaluation compared to those with lower values.

Due to its retrospective design, our study has some limitations. All patients had complete blood count test, whereas only 67 of 119 patients had CRP values. Although we excluded the patients with laboratory tests that had not evaluated in the six hours, the exact timing of the caustic damage was not assessed because the data for all patients were not complete. Number of patients with severe injury was low according to mild-moderate patients in our study. This is the first study evaluating NLR in caustic injuries which was used for diagnosis and predictor of course in many diseases.

In conclusion, NLR has a significant association with organ involvement and grade of involvement. It is an easily derived, inexpensive and widely available marker of inflammation. Elevated NLR levels may be a marker of severe caustic injuries and widespread involvement. Thus, it could be an effective guide for the management of patients before endoscopic evaluation in Emergency Departments. However, further prospective controlled studies with larger populations are needed in this subject.

## References

1. Patrick R, Shawn M (2016) Foreign Bodies, Bezoars, and Caustic Ingestions, In: Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt (Eds). *Sleisenger & Fordtran's Gastrointestinal & Liver diseases*. 10th edition, Saunders Elsevier Science, USA 2016, pp 426-438.
2. Contini S, Scarpignato C (2013) Caustic injury of the upper gastrointestinal tract: a comprehensive review. *World J Gastroenterol* 19: 3918-3930.
3. Cattan P, Munoz-Bongrand N, Berney T, Halimi B, Sarfati E, et al. (2000) Extensive abdominal surgery after caustic ingestion. *Ann Surg* 231: 519-523.
4. McAuley CE, Steed DL, Webster MW (1985) Late sequelae of gastric acid injury. *Am J Surg* 149: 412-415.
5. Poley JW, Steyerberg EW, Kuipers EJ (2004) Ingestion of acid and alkaline agents: outcome and prognostic value of early upper endoscopy. *Gastrointest Endosc* 60: 372-377.
6. Katzka DA (2001) Caustic Injury to the Esophagus. *Curr Treat Options Gastroenterol* 4: 59-66.
7. Ryu HH, Jeung KW, Lee BK (2010) Caustic injury: can CT grading system enable prediction of esophageal stricture? *Clin Toxicol (Phila)*. 2010;48: 137-142.
8. Chiu HM, Lin JT, Huang SP (2004) Prediction of bleeding and stricture formation after corrosive ingestion by EUS concurrent with upper endoscopy. *Gastrointest Endosc* 60: 827-833.
9. Cheng YJ, Kao EL (2003) Arterial blood gas analysis in acute caustic ingestion injuries. *Surg Today* 33: 483-485.
10. Imtiaz F, Shafique K, Mirza SS (2012) Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 5: 2.
11. Balta S, Celik T, Mikhailidis DP (2016) The Relation Between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. *Clin Appl Thromb Hemost* 22: 405-411.
12. Isaac V, Wu CY, Huang CT (2016) Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. *Medicine (Baltimore)* 95: e3832.
13. Gibson PH, Croal BL, Cuthbertson BH (2007) Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J* 154: 995-1002.
14. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ (2005) Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 91: 181-184.
15. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, et al. (2009) Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 137: 425-428.
16. Sharaiha RZ, Halazun KJ, Mirza F (2011) Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol* 18: 3362-3369.
17. Zargar SA, Kochhar R, Mehta S, Mehta SK (1991) The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 37: 165-169.
18. Betalli P, Falchetti D, Giuliani S (2001) Caustic Ingestion Italian Study Group. Caustic ingestion in children: is endoscopy always indicated? The results of an Italian multicenter observational study. *Gastrointest Endosc* 68: 434-439.
19. Kaya M, Ozdemir T, Sayan A (2010) The relationship between clinical findings and esophageal injury severity in children with corrosive agent ingestion. *Ulus Travma Acil Cerrahi Derg* 16: 537-540.
20. Chen TY, Ko SF, Chuang JH (2003) Predictors of esophageal stricture in children with unintentional ingestion of caustic agents. *Chang Gung Med J* 26: 233-239.
21. Havanond C, Havanond P (2007) Initial signs and symptoms as prognostic indicators of severe gastrointestinal tract injury due to corrosive ingestion. *J Emerg Med* 33: 349-353.
22. Rigo GP, Camellini L, Azzolini F, Guazzetti S, Bedogni G, et al. (2002) What is the utility of selected clinical and endoscopic parameters in predicting the risk of death after caustic ingestion? *Endoscopy* 34: 304-310.
23. Cabral C, Chirica M, de Chaisemartin C (2012) Caustic injuries of the upper digestive tract: a population observational study. *Surg Endosc* 26: 214-221.